Remarks/Arguments

Prior to the present amendments, claims 13-17, 38, 40 and 44 were pending in this application and stood rejected on various grounds. Claims 13-15, and 38 have been canceled, and claims 16, 40 and 44 have been amended. The amendments are of formal nature and are fully supported by the specification as originally filed. All amendments and cancellations were made without prejudice or disclaimer. Applicants explicitly reserve the right to pursue any deleted subject matter in one or more continuing applications.

Claim Objections

Claims 14 and 44 have been objected to due to their recitation of the phrases "polypeptide of SEQ ID NO: 3" and "polypeptide of SEQ ID NO: 6." The Examiner has suggested that this should be corrected to: "polypeptide comprising the amino acid sequence of SEQ ID NO: 3" and "polypeptide comprising the amino acid sequence of SEQ ID NO: 6."

Claim 14 has been canceled, which moots its rejection. Claim 44 has been amended essentially following the Examiner's suggestion, which is believed to obviate its rejection.

Claim Rejections – 35 USC § 112, first paragraph - enablement

Claims 13-17, 21, 38 and 40 were rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner acknowledges that "there may be an association between Wnt-1 expression and clone 65 polypeptide," and that the specification "has . .. shown this association . . . for two specific polypeptides, that of a polypeptide comprising the amino acid sequence of SEQ ID NO: 3 and comprising the amino acid sequence of SEQ ID NO: 6." (Office Action, page 4) Thus, the finding of non-enablement is based on two assertions: (1) it has not been shown that polypeptides having at least 90% sequence identity to SEQ ID NO: 3 or SEQ ID NO: 6 are differentially expressed in Wtn-1 associated cancer, and (2) "an association between Wnt-1 expression and clone 65 expression does not provide evidence that clone 65 polypeptides may be used as diagnostic markers." (Office Action, page 4)

Claims 13-15, and 38 have been canceled, which moots their rejection. The rejection of the remaining claims is respectfully traversed.

Since, without acquiescence to the Examiner's position, the claims no longer encompass variants of clone 65 polypeptides, the first reason for the finding of lack of enablement falls. As far as the second reason is concerned, Applicants strongly disagree with the Examiner's position.

As explained in Applicants' response to a previous similar rejection, the invention claimed in the present application is based on the identification and isolation of a new member of the Rho protein family, designated clone 65. Human clone 65 shares around 59% sequence identity with CDC42, a well characterized member of the Rho family. Rho family proteins were known at the priority date of this application to contribute to the transforming actions of certain oncoproteins. For example, it was known that the Ras oncoproteins require Rho family protein function to cause growth transformation, as stated on page 3, lines 29-32 of the application as filed. It was also known that aberrant activation of Rho family proteins can cause growth transformation, invasion, and metastasis in experimental models of carcinogenesis, which are responses typical of neoplasia (see, e.g. the passage bridging pages 3 and 4 of the specification).

In their previous response, Applicants introduced numerous scientific papers is further support of the association between clone 65 (Wrch-1) and Wnt-1. In particular, Applicants submitted the following evidence of the involvement of clone 65/Wrch-1 in cancer:

(1) *The expression of clone 65/Wrch-1 is induced upon activation of the Wnt-1 pathway*

The disclosure of the present application and Tao *et al., Genes & Development* 15:1796-1807 (2001) experimentally show that the expression of clone 65/Wrch-1 is induced upon activation of the Wnt-1 pathway. Since the involvement of the Wnt-1 pathway in cancer was well known in the art at the priority date of the present application, this alone provides a strong indication that clone65/Wrch-1 is similarly involved.

(2) *Clone 65/Wrch-1 activates PAK-1 and JNK-1*

Tao *et al., Genes & Development* 15:1796-1807 (2001) also show that clone 65/Wrch-1 activated PAK-1 and JNK-1. Similarly, Kumar et al., *Nature Reviews/Cancer* 6:459-471 (2006) confirm that the expression of clone 65/Wrch-1 is induced by Wnt-1, and that Wrch-1 is an activator of PAK-1.

Since PAK-1 (which is activated by clone 65/Wrch-1) is known to be involved in cancer, and is overexpressed in 55% of human breast cancer (see, Carter et al., *Clinical Cancer Research* 10:3448-3456 (2004), and JNK-1 (which is also activated by clone 65/Wrch-1) has been implicated in transformation and progression in numerous tumors including prostate cancer (Potapova et al., *Cancer Res.* 62:3257-3263 (2002)); breast cancer (O'Hagan and Hassell, *Oncogene* 16:301-310 (1998)) and lung cancer (Bost et al., *J. Biol. Chem.* 272:33422-33429 (1997)), the experimental finding that clone 65/Wrch-1 activated PAK-1 and JNK-1 is further evidence of the involvement of clone 65/Wrch-1 in cancer.

(3) *The expression of Wnt-1 is increased in response to Wnt-1*

Applicants additionally submitted Taneyhill and Pennica, *BMC Developmental Biology* 2004, 4:6 (2004), co-authored by one of the inventors of the present application, providing experimental evidence that the expression of the Wrch-1 gene increased 3.2-fold in Wnt-1 treated samples, and that this gene has been confirmed to be truly Wnt-1 responsive. This is additional evidence of the involvement of clone 65/Wrch-1 in cancer.

It is noteworthy that the Examiner did not comment on any of the scientific publications submitted by Applicants, except Kumar et al., of which the Examiner states:

> *"Applicants point to the teachings of Kumar as clearly indicating the involvement of Wrch-1 in the regulation of cancer cells by PAK-1. A review of Kumar does not appear to provide this reaching because there does not appear to be even one mention of Wrch-1 . .. "* (Office Action, page 4, emphasis added.)

The Examiner's statement is clearly in error, since, as it was quoted in Applicants' previous response, Kumar at page 463, first column confirms that Wrch-1 expression is induced by Wnt-1 and Wnt-1 is, in turn, an activator of PAK-1. Although in the Kumar review article

Wrch-1 is spelled "WRCH1" there can be no doubt that the two designations mean the same protein, and thus the Examiner's statement is factually incorrect.

In conclusion, the submitted evidence (seven pier reviewed scientific papers) clearly confirms the involvement of clone 65/Wrch-1 in the pathology of cancers involving the Wnt-1 pathway, and thus, clone 65/Wrch-1 find utility in the diagnosis of Wnt-1 and PAK-1 associated cancers. Applicants submit that the specification, when read by one of ordinary skill in the art, clearly enables this use, and thus the present rejection is misplaced.

It is submitted that, based on the disclosure of the present application and general knowledge in the art, one of ordinary skill in the art would clearly know how to use the clone 65/Wrch-1 polypeptides of the present invention in the diagnosis of cancer. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 USC § 112, first paragraph – written description

Claims 13, 16, 17 and 38 have been rejected under 35 U.S.C. 112, first paragraph as allegedly failing to comply with the enablement requirement. According to the rejection, the specification fails to provide adequate written description for polypeptides that have at least 90% sequence identity to the sequence of SEQ ID NO: 3 or SEQ ID NO: 6.

Without acquiescing to this rejection, claims 13 and 38 have been canceled, and claims 16 and 17 no longer recite amino acid sequence variants of SEQ ID NO: 3 or SEQ ID NO: 6. Accordingly, this rejection is believed to be moot.

Claims Rejections – 35 USC § 102

Claims 13, 16 and 38 were rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Hillman (US 5,840,569). According to the rejection, Applicants' argument that the polypeptide of Hillman has only 74% sequence identity with SEQ ID NO: 3 is not persuasive, since "the claims do not recite that the percent identity is over the entire length of the polypeptide."

Without acquiescing to the present rejection, claims 13 and 38 have been canceled, and claim 16 no longer recites amino acid sequence variants of SEQ ID NO: 3, which obviates the present rejection.

It is submitted that all claims pending in this application are in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any fees, including fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39766-0157R1C1**).

Respectfully submitted,

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